

Adrenoleukodystrophy

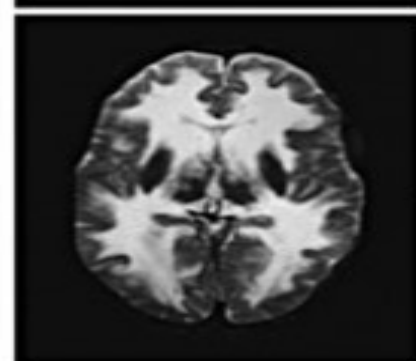
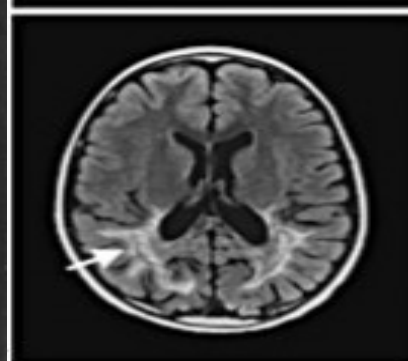
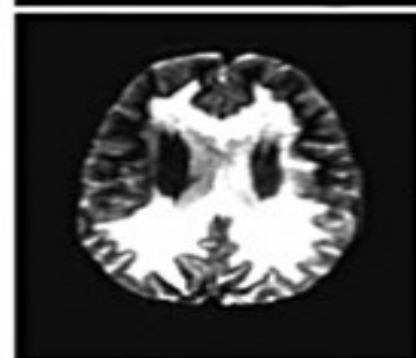
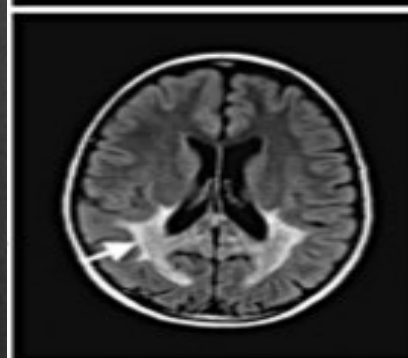
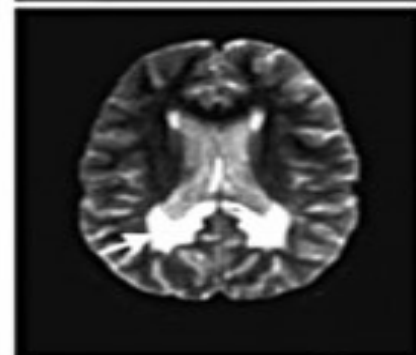
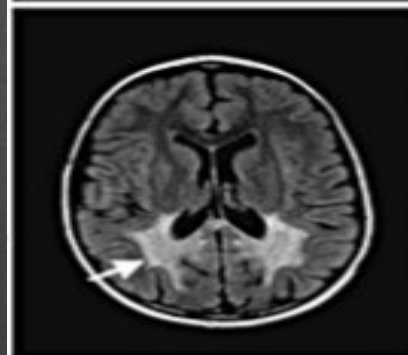
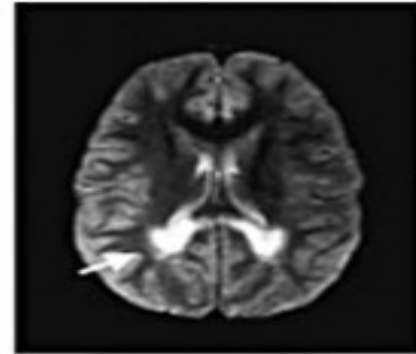
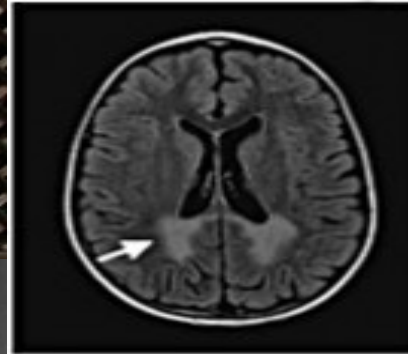
Jennifer Kallini

**Professor Doug Brutlag — Genomics and
Medicine**



• Paul Schilder 1913

• “ALD-X” coined in 1970



Symptoms

Behavioral:

- ADHD
- Apathy
- Irritability

Neurological

- Hearing, vision problems – Poor handwriting
- Ataxia
- Spasticity
- Paralysis
- Seizures

Endocrine

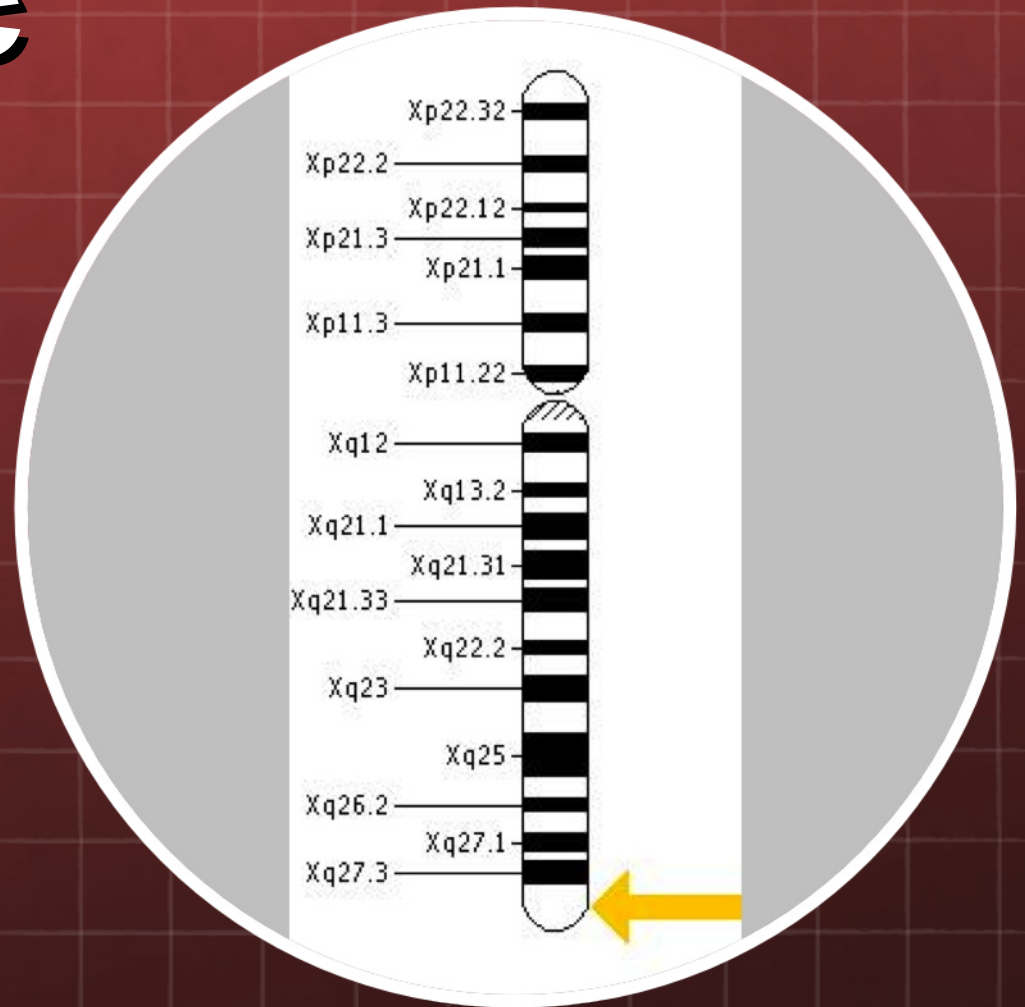
- Adrenal insufficiency

Incidence

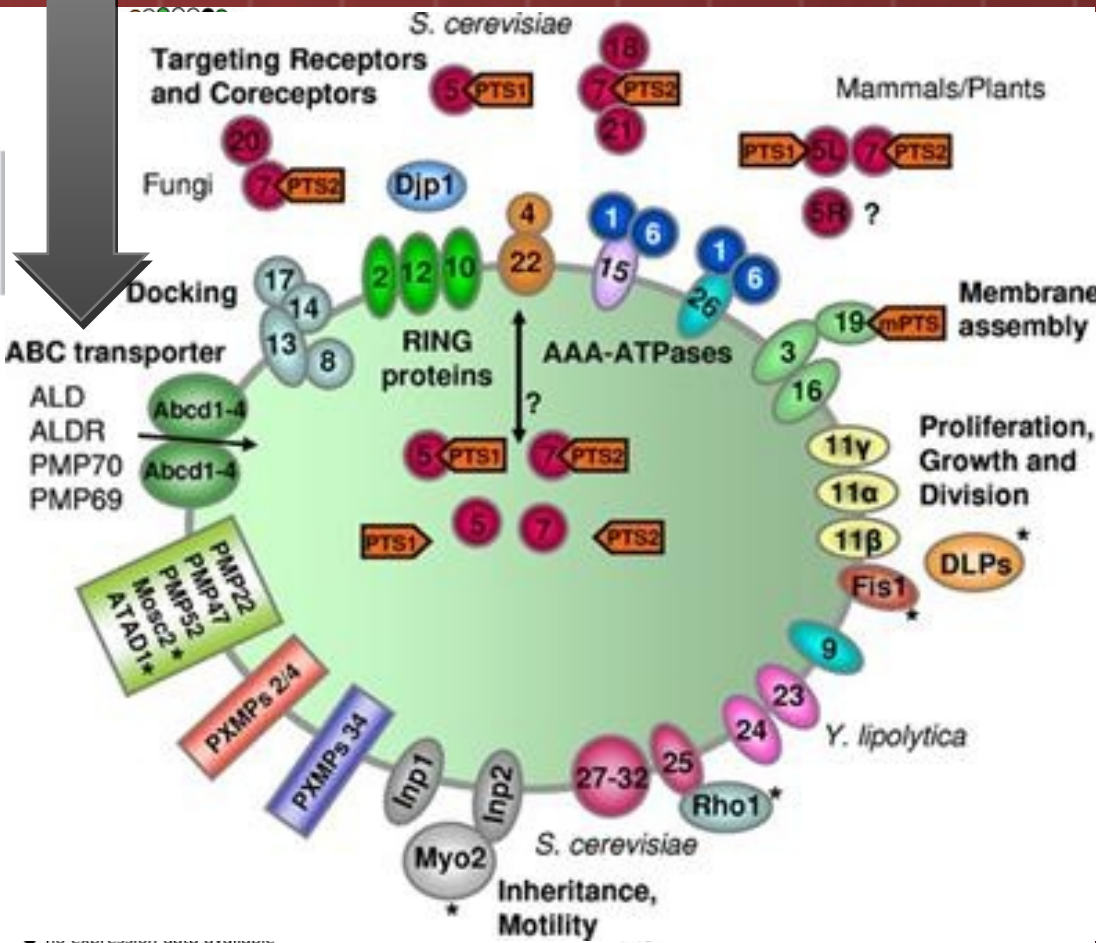
- **Estimated between 1 : 20,000 and 1 : 100,000**
- **No apparent predilection for any one race**
 - **Afro-Americans**
 - **Native Americans**
 - **Hispanics**
 - **Jews**
 - **Chinese**
 - **Japanese**
 - **Maoris**

Genetic S

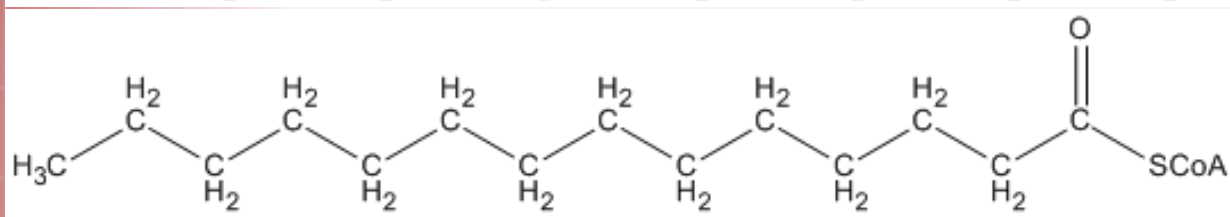
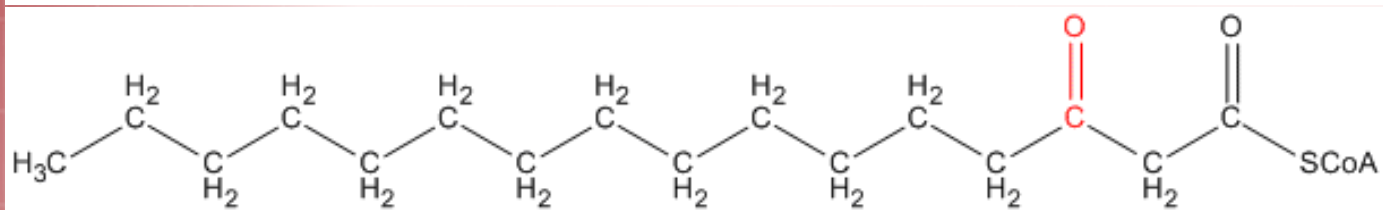
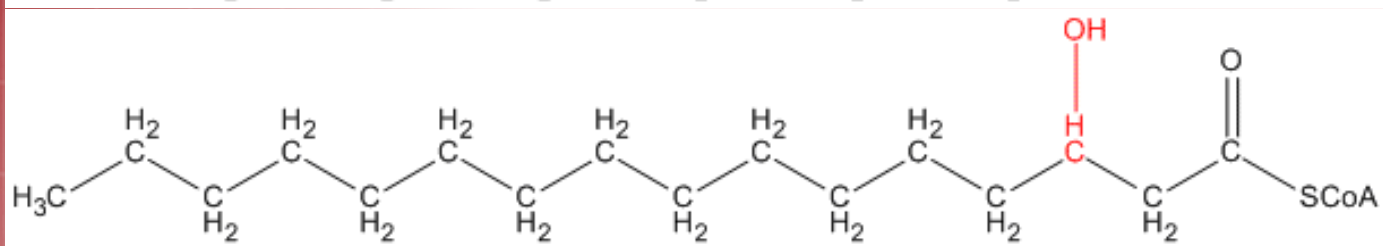
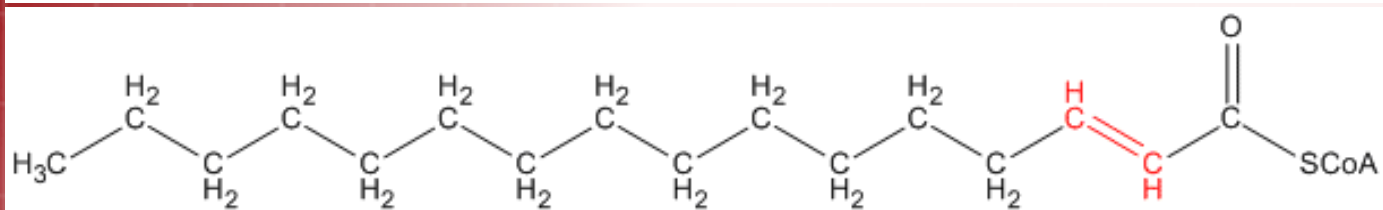
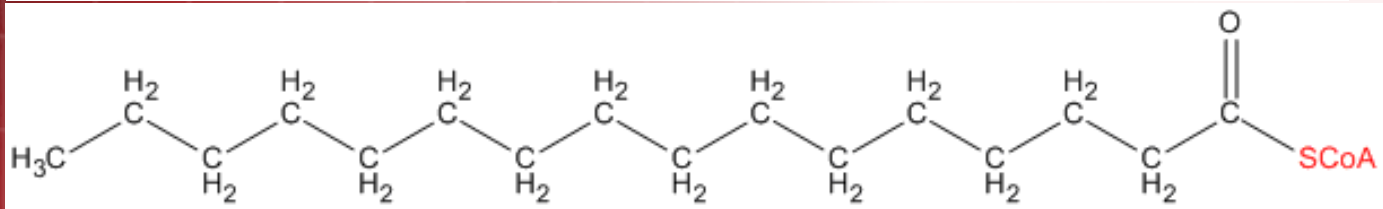
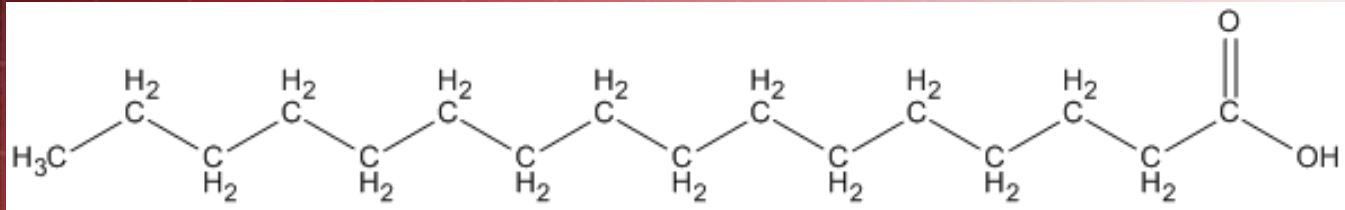
- **Mutation in ABCD1 gene (20kb)**
 - **Xq28**
 - **480 identified point mutations**



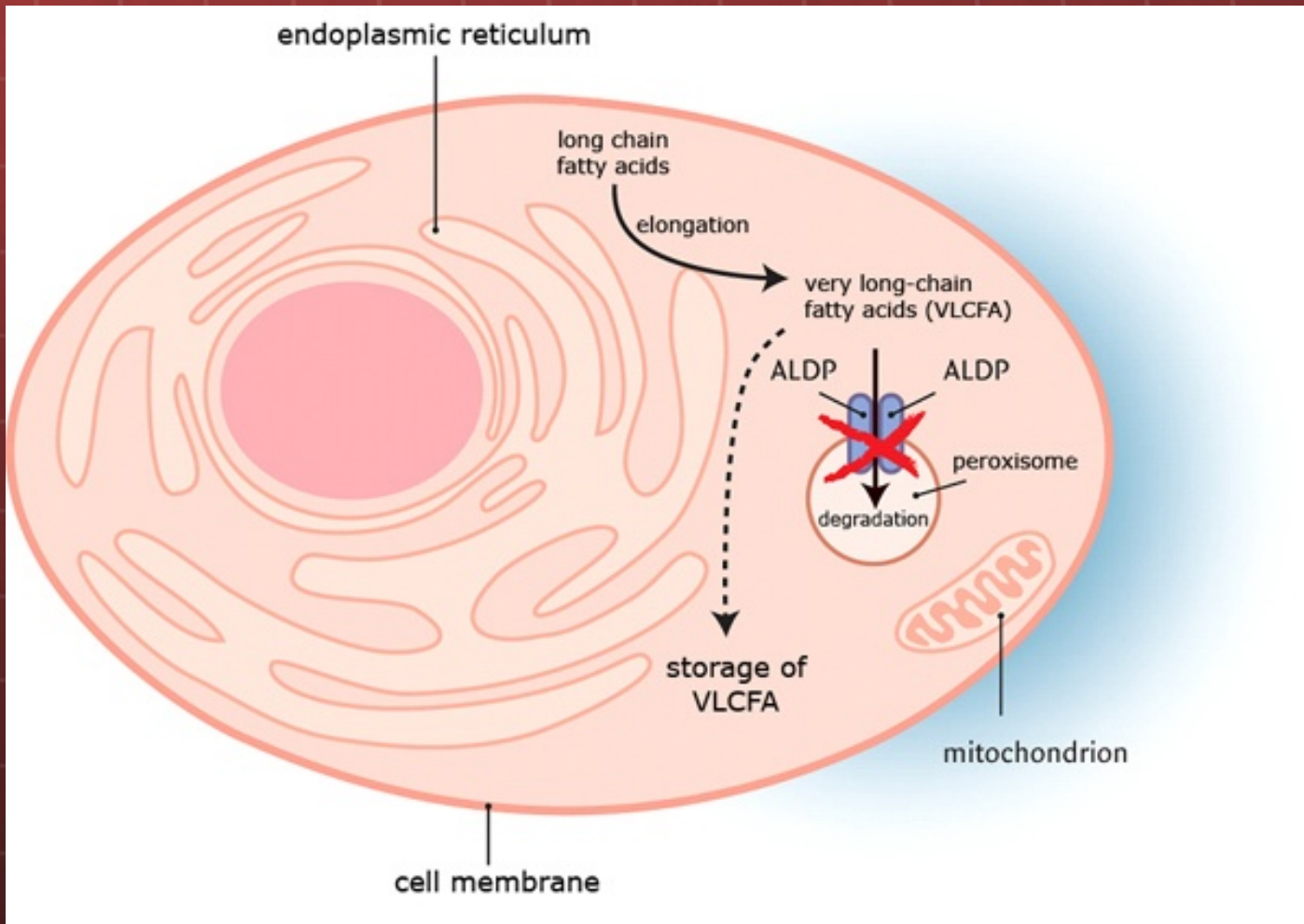
Homologous ATP-Binding Cassettes



- ALD-related protein
- 66% amino acid identity with ALDP
- PMP70 protein
- 38% amino acid identity with ALDP
- PMP70-related protein (P70R)
- 27% amino acid identity with ALDP



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A



V
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A

1. Whitcomb, *et al* study in 1988
 - a. Studied ACTH-stimulated cortisol release in human adrenocortical cells.
 - Added C26: 0 or C24: 0 (common VLCFAs that accumulate in patients with ALD-X) to cultured cells

CONCLUSION: Excess VLCFA altered membrane structure, and this is likely the cause

Why is the accumulation of VLCFA harmful?

2. Powers, *et al* study in 1980
 - a. Morphological and cytochemical study done using MRI's and MRS's
 - Found that adrenal dysfunction in individuals with ALD-X is due to accumulation of abnormal lipids that contain VLCFAs

CONCLUSION: Excess VLCFA is the cause of the adrenal insufficiency noted in patients with ALD-X

Why is the accumulation of VLCFA harmful?

Remaining questions:

No studies have, as of yet, been able to associate axonopathy with VLCFAs. However, researchers believe that axonopathy is due to the VLCFAs' disruption of axonal membranes, as was the case in adrenocortical cells.

→ A recent study by J. K. Ho, *et al* shows that incorporation of VLCFA in components of the multilamellar myelin membrane might indeed destabilize ALD myelin

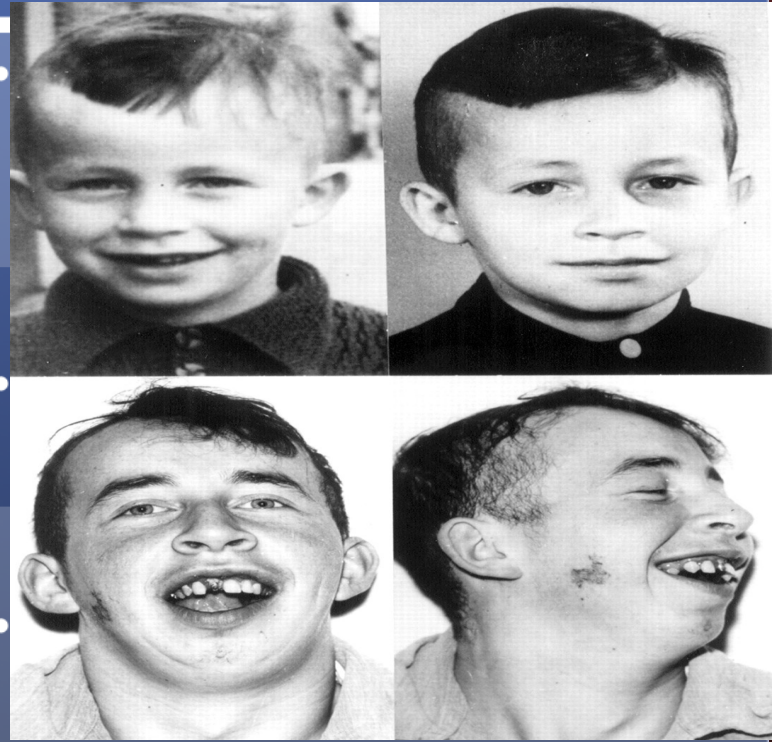
**Why is the
accumulation of
VLCFA harmful?**

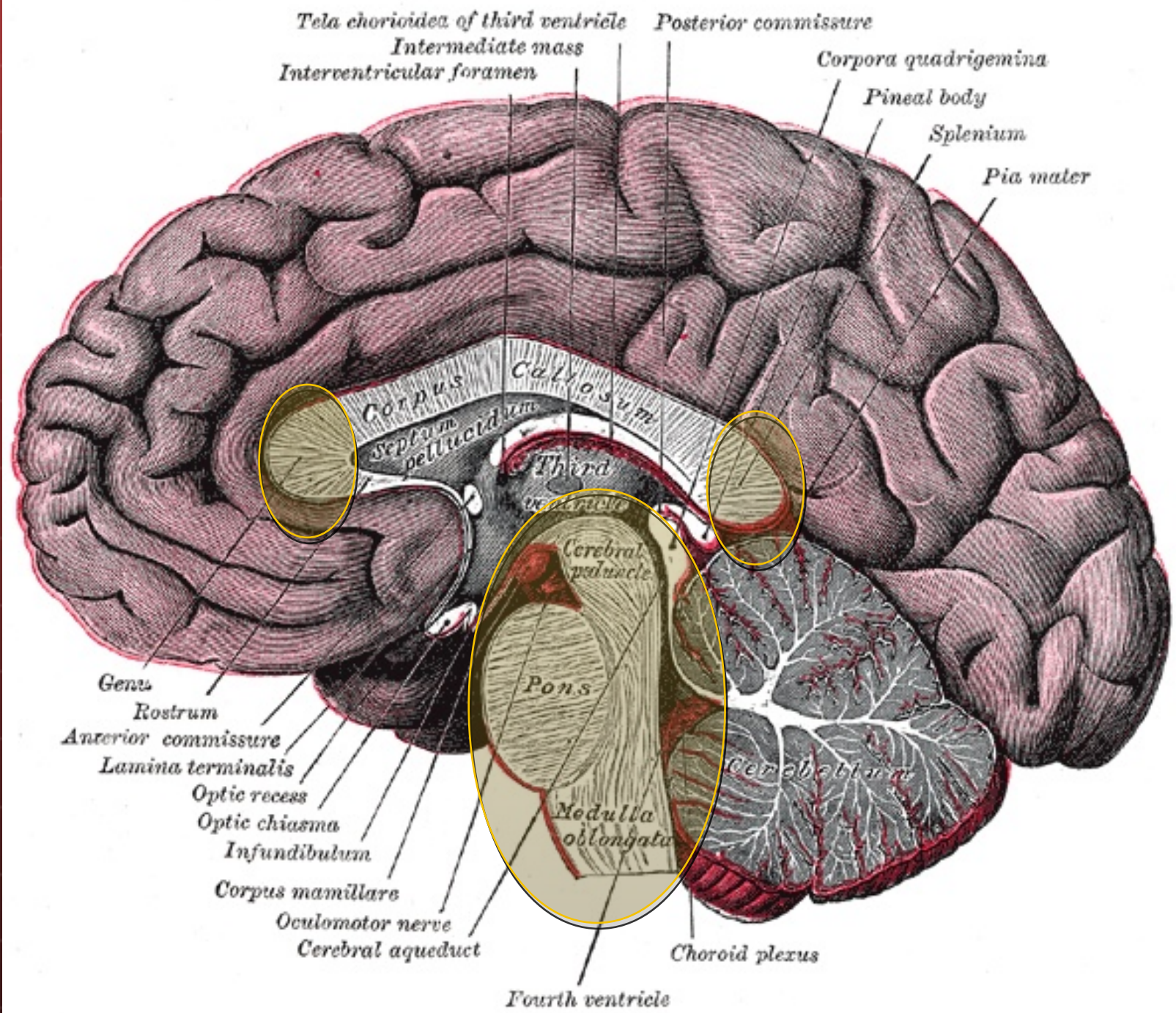
Types of ALD

Child-Onset ALD

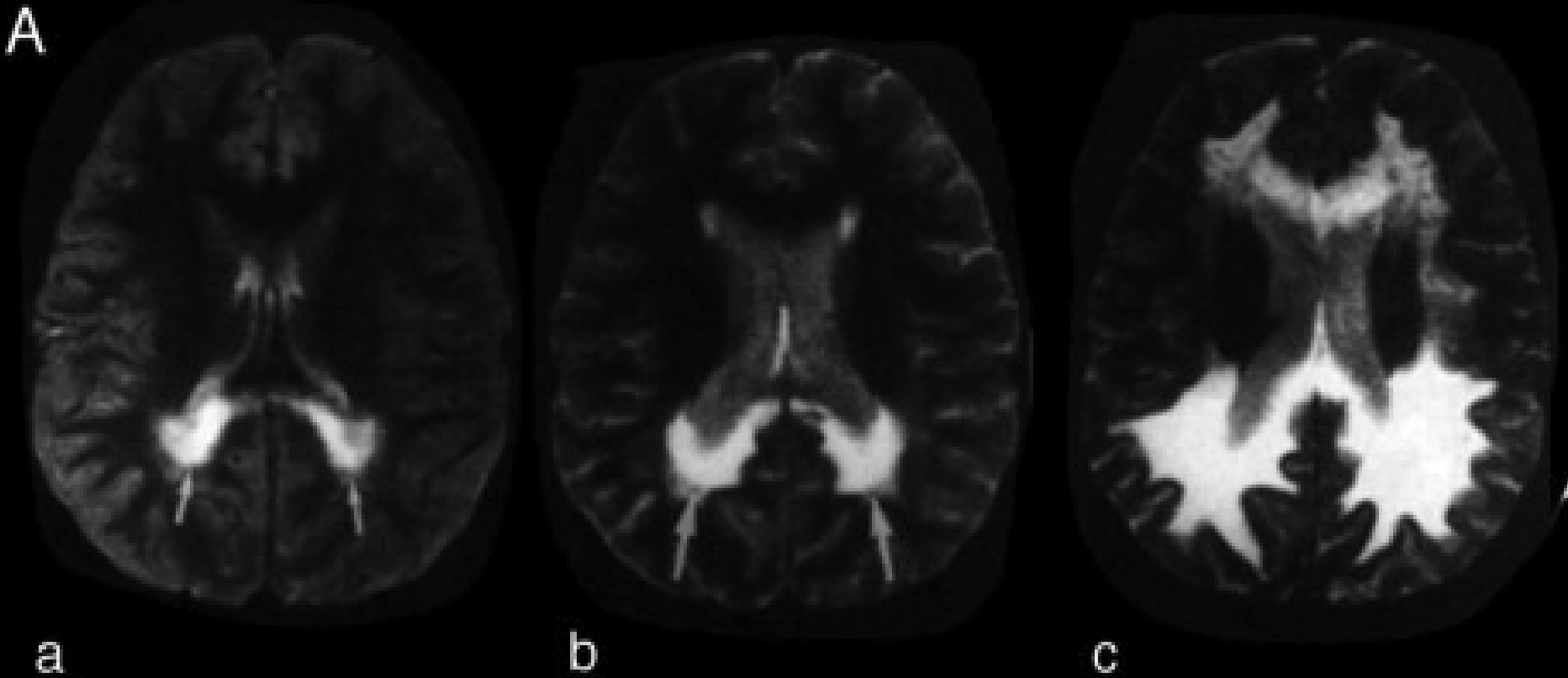


Adult-onset ALD





MRI scan showing the progression of demyelination in the parieto-occipital white matter over a period of three years in a child

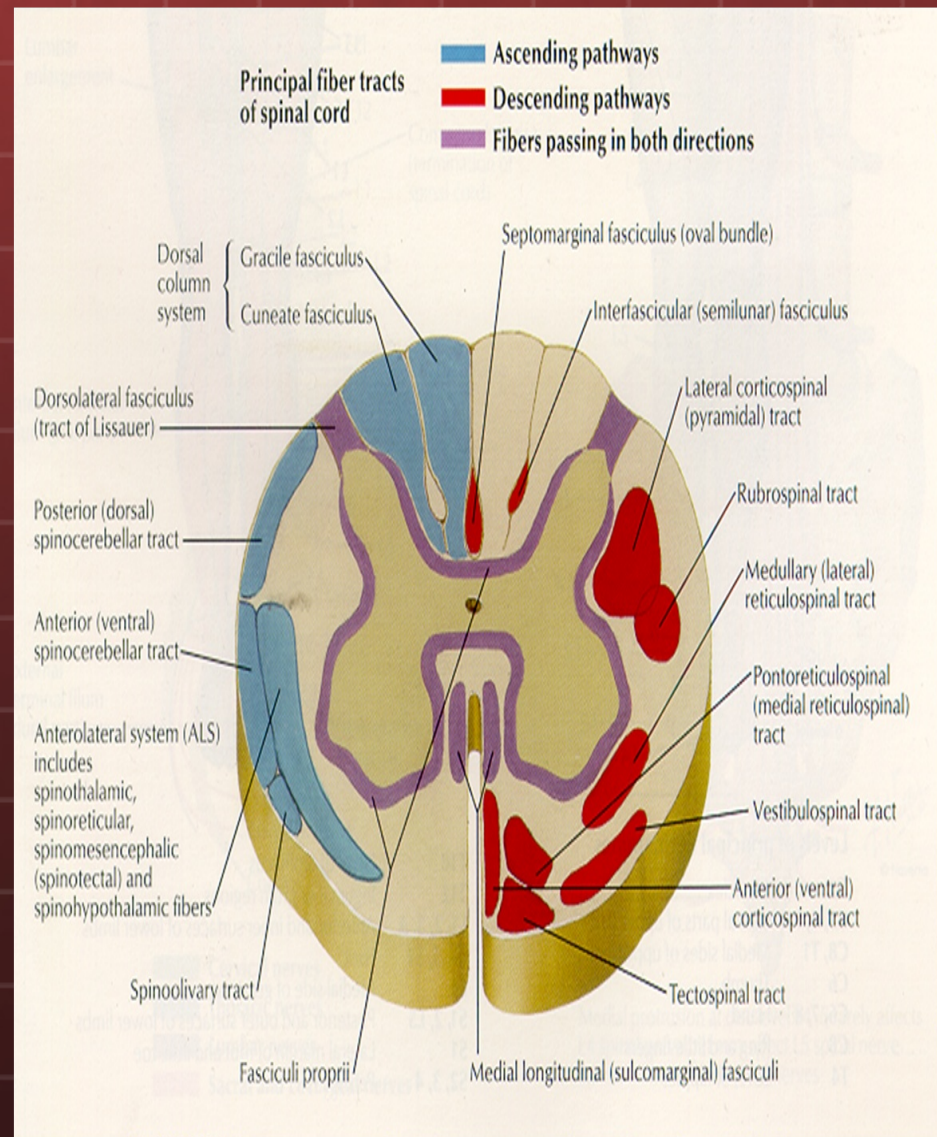


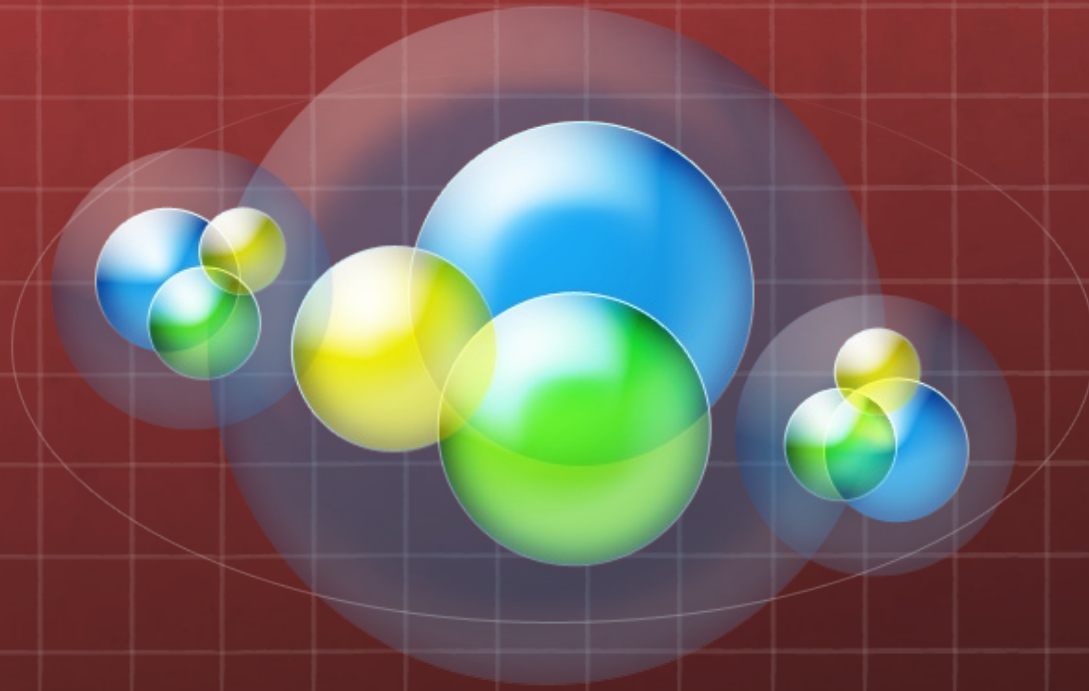
Peripheral Nerve Demyelination

- **Loss of axons and myelin throughout the:**

- **Anterior corticospinal tract**
- **Gracile tract**
- **Dorsal spinocerebellar tract**

- **Little inflammatory response**



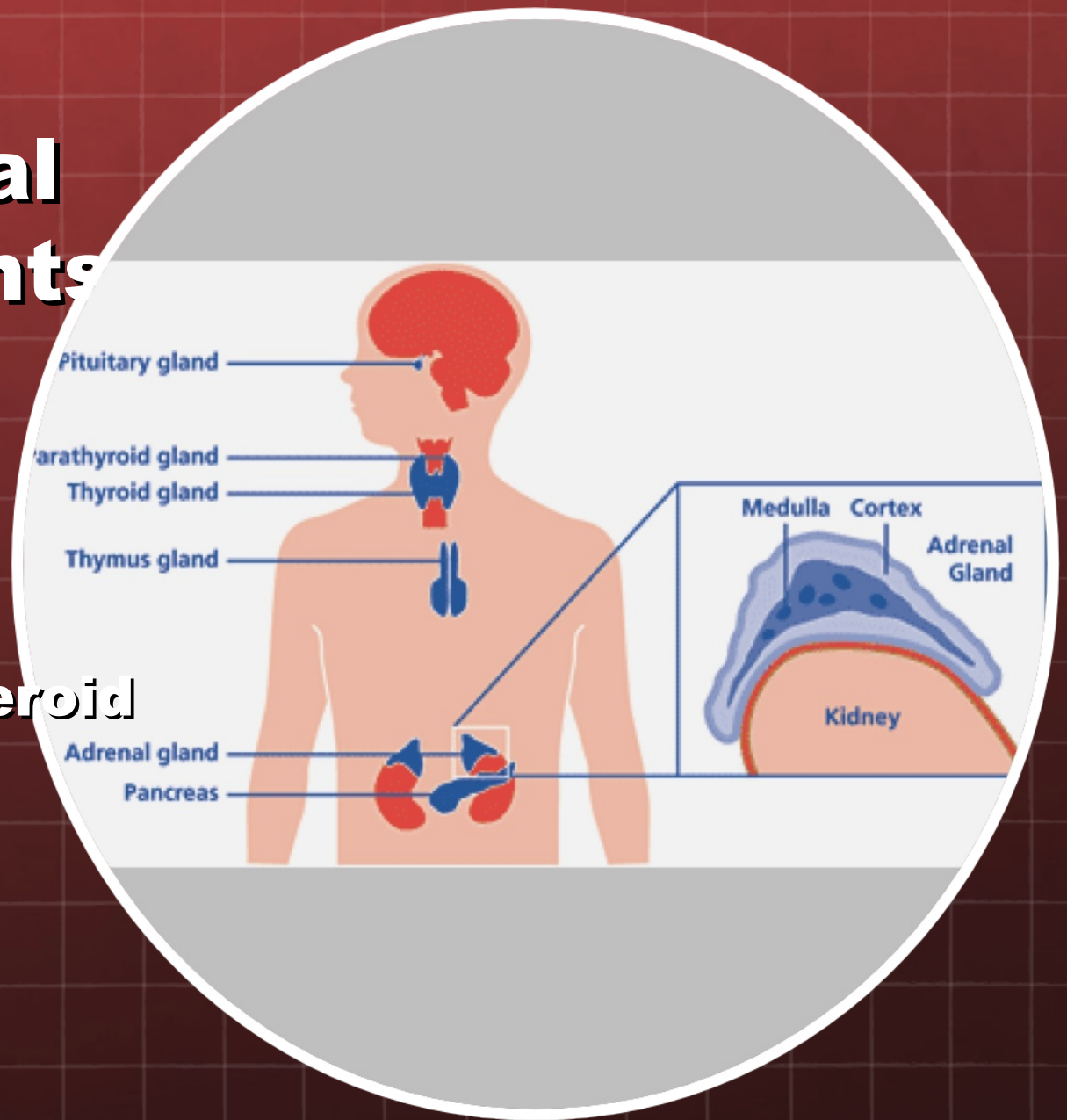


Treatments

Classical Treatments

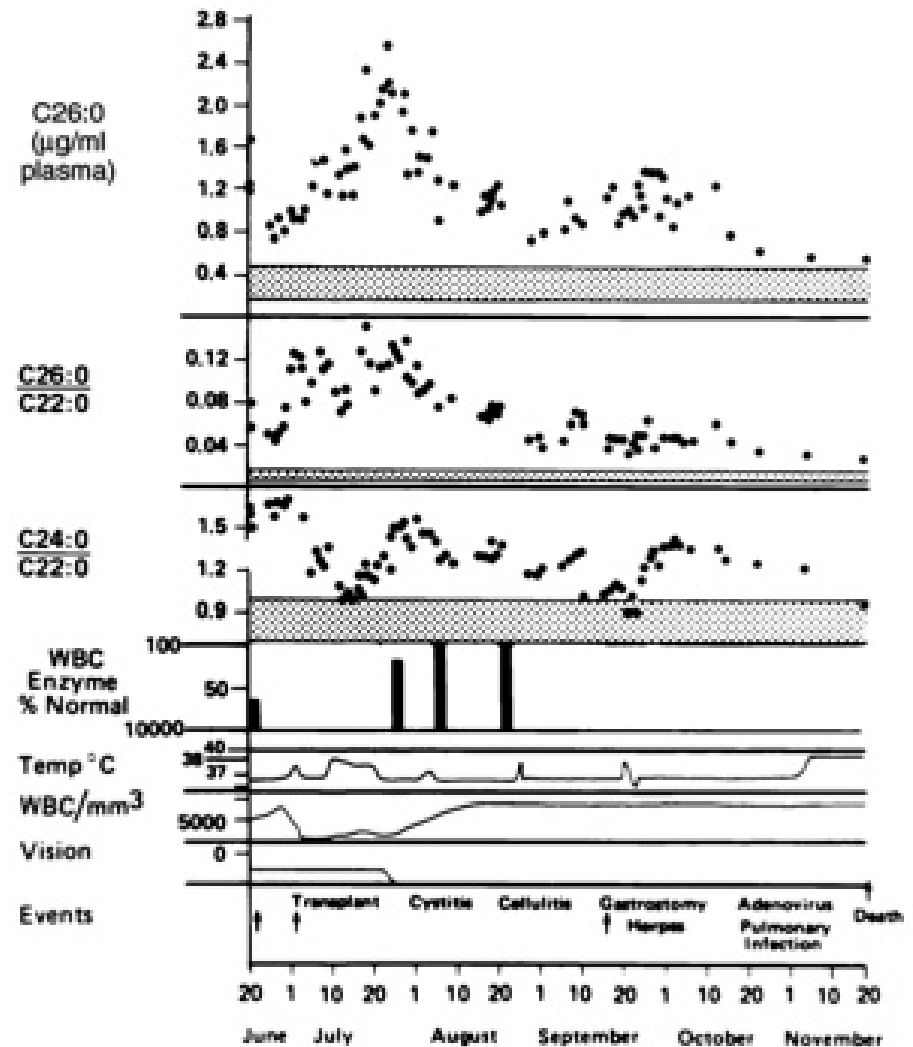
- Adrenal
insufficiency
therapy:

Treat with steroid
hormones

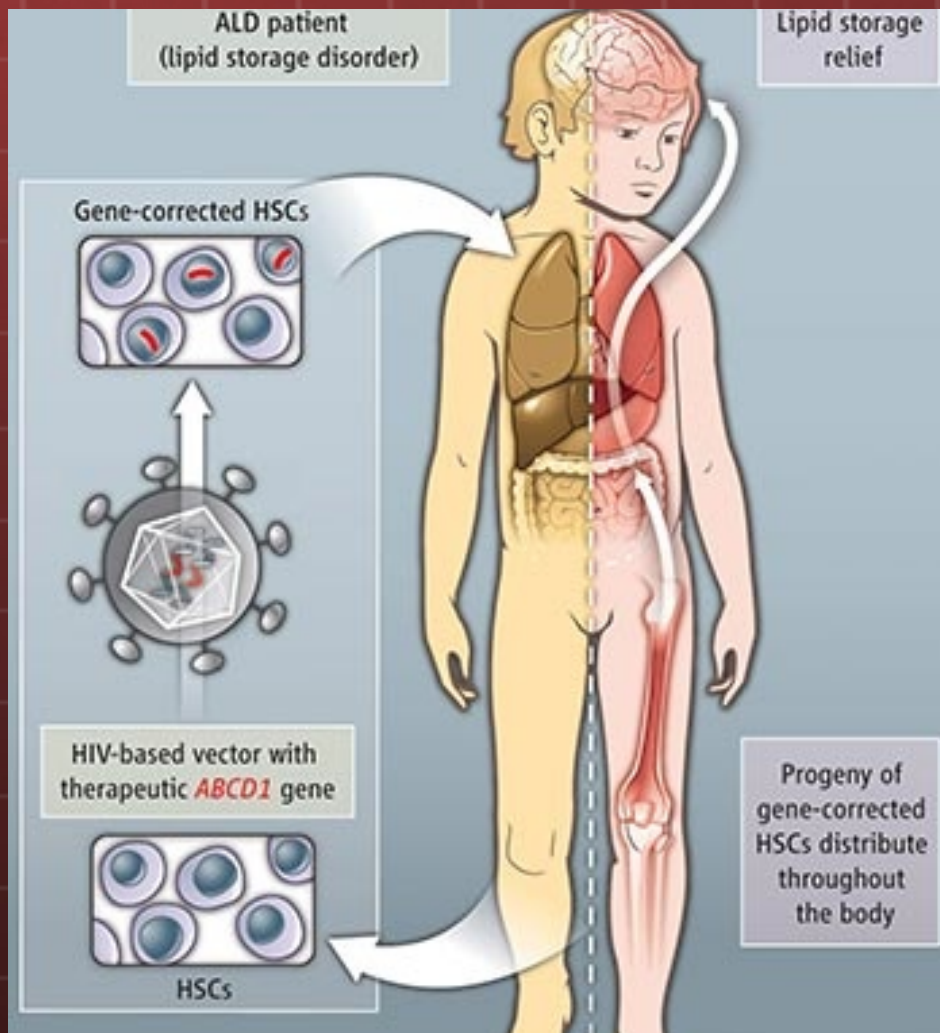


Classical Treatments

- **Bone Marrow Transplant**
 - Moser, *et al* 1984
 - Study done on a patient in the rapidly advancing stage of child-onset X-ALD
 - Promising effects: VLCFA levels diminished 2 months after transplant



Novel Treatment



- Gene Therapy
- Dr. Aubourg, 2009
- Able to correct 15% of a patient's hematopoietic stem cells

Drawbacks?



The end!
Please see notes
for references